CLAIMS

What is claimed is:

1. A method to aid in predicting susceptibility of a mammalian subject to development or growth of a steroid hormone responsive cancer in a mucosal epithelial tissue, the method comprising quantitating and/or detecting a steroid hormone reversible immunoglobulin inhibitor of steroid hormone responsive cell growth in a body fluid or secretion obtained from said subject, an absence or deficiency of said immunoglobulin inhibitor compared to a predetermined standard suggesting or indicating that a steroid hormone responsive mucosal epithelial tissue in said subject secretes or is bathed by less than a predetermined cell growth inhibitory amount of said immunoglobulin inhibitor.

2. The method of claim 1 further comprising obtaining a sample of body fluid or secretion chosen from the group consisting of serum, plasma, colostrum, breast aspirates, saliva, tears, bronchial secretions, nasal mucosa, prostatic fluid, urine, semen or seminal fluid, vaginal secretions, ovarian aspirates, stool, and mucous secretions from the small intestine or stomach.

3. The method of claim 1 wherein said quantitating and/or detecting comprises measuring the amount and/or activity of an immunoglobulin inhibitor in a specimen comprising a defined amount of body fluid or secretion from said subject.

4. The method of claim 1 wherein said quantitating and/or detecting comprises substantially depleting steroid hormone from said specimen to yield a steroid hormone depleted specimen, and assaying an aliquot of said steroid hormone depleted specimen for steroid hormone reversible inhibition of steroid hormone responsive cancer cell proliferation.

5. The method of claim 4 wherein said assaying comprises:

maintaining a predetermined population of steroid hormone-responsive cancer cells in a nutrient medium containing calcium ion and substantially no free ferric ion, said cells also being steroid hormone responsive for *in vivo* proliferation if implanted in a suitable host;

adding a predetermined amount of said steroid hormone to said medium, said amount being sufficient to stimulate cell growth under cell growth promoting culture conditions;

adding a predetermined amount of a steroid hormone free specimen of a body fluid or secretion to said medium, to yield a test mixture;

incubating said test mixture for a predetermined period of time under cell growth promoting conditions;

measuring the cell population in said test mixture after said predetermined period of time;

measuring the cell population in a control incubation mixture like said test mixture, except lacking an amount of said specimen;

optionally, testing said amount of specimen for cytotoxic effects on said cells;

measuring the differences between said cell populations before and after said incubation period, a significant increase in said cell population indicating the absence of inhibition of cell growth by said amount of specimen in the presence of said predetermined amount of steroid hormone, and a significant lack of increase in said cell population not attributable to cytotoxic effects of said amount of specimen indicating inhibition of cell growth by said amount of specimen in the presence of said predetermined amount of steroid hormone.

6. The method of claim 5 wherein said predetermined amount of steroid hormone is in the physiological concentration range for said steroid hormone in said mammal.

7. An *in vitro* method of detecting loss of immunoglobulin regulation of steroid hormone responsive cell growth comprising assaying for inability of a mucosal epithelial cell to bind at least one immunoglobulin chosen from the group consisting of IgA, IgM and IgG1.

8. A method of detecting a mediator of immunoglobulin inhibition of steroid hormone responsive cell growth comprising detecting a poly-Ig receptor or a Fcγ receptor in a mucosal epithelial cell, said receptor being capable of mediating steroid hormone reversible immunoglobulin inhibition of steroid hormone responsive cell growth in a suitable *in vitro* cell culture assay.

9. A method of detecting a gene coding for a mediator of immunoglobulin inhibition of steroid hormone responsive cell growth comprising detecting the presence of a poly-Ig receptor gene or a Fcγ receptor gene in a mucosal epithelial cell.

10. A method of detecting a genetic defect in a gene coding for a mediator of immunoglobulin inhibition of steroid hormone responsive cell growth comprising screening a genomic or cDNA library of a mucosal epithelial cell for a defect in a poly-Ig receptor gene or a Fcγ receptor gene.

11. A method of detecting expression of a defective mediator of immunoglobulin inhibition of steroid hormone responsive cell growth in a specimen of mucosal epithelial tissue, the method comprising detecting a defective poly-Ig receptor or a Fcγ receptor in said specimen.

12. A method to aid in predicting susceptibility of a mammalian subject to development of breast cancer comprising detecting the loss or impairment of negative regulation of breast tissue proliferation by the secretory immune system in said subject.

13. A method to aid in predicting increased susceptibility of a mammalian subject to development or growth of a steroid hormone responsive cancer in a mucosal epithelial tissue, the method comprising assaying a specimen of mucosal epithelial tissue obtained from said subject for the presence of a poly-Ig receptor capable of mediating steroid hormone reversible immunoglobulin inhibition of steroid hormone responsive cell growth in a suitable *in vitro* cell culture assay, an absence of said receptor or an absence of activity of said receptor for mediating said immunoglobulin inhibition suggesting that said tissue lacks sufficient functional mediators of immunoglobulin inhibition to deter development or growth of a steroid hormone responsive cancer in said mucosal epithelial tissue.

14. A method to aid in detecting transformation of a mucosal epithelial cell from normally steroid hormone responsive to a steroid hormone responsive cancerous condition, the method comprising assaying a population of said cells for loss or inactivity of a receptor that mediates IgG1 inhibition of cell growth.

15. A method to aid in detecting progression of a steroid hormone responsive malignant mucosal epithelial cell to an autonomous cancer cell, the method comprising testing said cell for loss or inactivity of a receptor that mediates IgA and/or IgM inhibition of steroid hormone responsive cancer cell growth.

16. A method of imaging a steroid hormone responsive mucosal epithelial tumor *in vivo* comprising contacting said tumor with at least one tagged monoclonal antibody raised against a protein chosen from the group consisting of poly-Ig receptor, Fcγ receptor, IgA, IgM and IgG1; and detecting said tag.

17. A method to aid in detecting or diagnosing cancer in a mammalian subject comprising determining, in a population of cells taken from a mucosal epithelial tissue specimen obtained from said subject, at least one of a first set of conditions selected from the following:

absence or diminution of immunoglobulin inhibition of steroid hormone responsive cell growth,

absence or diminution of at least one immunoglobulin inhibitor of steroid hormone responsive cell growth from a body fluid or secretion secreted by or bathing said tissue,

absence or diminution of a poly-Ig receptor in said cells,

absence of a poly-Ig receptor gene from said cells,

absence of heterozygosity for said poly-Ig receptor gene in said cells,

absence or diminution of a Fcγ receptor in said cells,

absence of a Fcγ receptor gene from said cells,

absence of heterozygosity for said Fcγ receptor gene in said cells,

and, optionally, detecting at least one of a second set of conditions selected from the following:

absence or diminution of TGFβ regulation of cell growth,

absence or diminution of a TGFβ receptor in said cells,

absence of a TGFβ receptor gene from said cells,

absence of heterozygosity for said TGFβ receptor gene in said cells,

said absence or diminution being measured by comparison to similar determinations in non-neoplastic cells from said patient and/or to the patient's previous test results, or by comparison to a predetermined standard value, the presence of at least one said condition being suggestive or indicative of the presence of a cancerous or precancerous lesion in said patient, and an absence of one or more of said conditions being suggestive or indicative of the absence of a cancerous or precancerous lesion in said patient.

18. A method to aid in staging a cancer of a mucosal epithelial tissue comprising:

determining, in a specimen of neoplastic cells obtained from said cancer, if said cells are stimulated by a preselected steroid hormone to proliferate in a suitable cell growth nutrient medium; and determining at least one of the following conditions:

in a specimen of body fluid or secretion secreted by or bathing said mucosal epithelial tissue, the lack of a cell growth inhibitory amount of at least one immunoglobulin inhibitor of steroid hormone responsive cell growth,

loss or diminution of a TGFβ receptor in said cells,

loss of a TGFβ receptor gene in said cells in said cells,

loss of heterozygosity for said TGFβ receptor gene in said cells,

loss or diminution of a poly-Ig receptor in said cells,

loss of a poly-Ig receptor gene in said cells,

loss of heterozygosity for said poly-Ig receptor gene in said cells,

loss or diminution of a Fcγ receptor in said cells,

loss of a Fcγ receptor gene in said cells,

loss of heterozygosity for said Fcγ receptor gene in said cells,

said loss or diminution being measured by comparison to similar determinations in non-neoplastic cells from said patient and/or to the patient's previous test results, or by comparison to predetermined standard

values, the presence of one or more of said conditions being suggestive or indicative of an advance in cancer stage.

19. A method to aid in prognosis of a mammalian cancer patient comprising determining at least one of the following conditions:

in a specimen of body fluid or secretion secreted by or bathing a mucosal epithelial tissue obtained from said patient, the lack of a cell growth inhibitory amount of at least one immunoglobulin inhibitor of steroid hormone responsive cell growth,

in a specimen of neoplastic cells from said tissue, the loss or diminution of a TGFβ receptor,

in a specimen of neoplastic cells from said tissue, the loss of a TGFβ receptor gene,

in a specimen of neoplastic cells from said tissue, the loss of heterozygosity for said TGFβ receptor gene,

in a specimen of neoplastic cells from said tissue, the loss or diminution of a poly-Ig receptor,

in a specimen of neoplastic cells from said tissue, the loss of a poly-Ig receptor gene,

in a specimen of neoplastic cells from said tissue, the loss of heterozygosity for said poly-Ig receptor gene,

in a specimen of neoplastic cells from said tissue, the loss or diminution of a Fcγ receptor,

in a specimen of neoplastic cells from said tissue, loss of a Fcγ receptor gene,

in a specimen of neoplastic cells from said tissue, loss of heterozygosity for said Fcγ receptor gene, said loss or diminution being determined by comparison to similar determinations in non-neoplastic cells from said patient or by comparison to defined standard values, the presence of one or more of said conditions being suggestive or indicative of at least some degree of reduced prognosis of said patient, and an absence of one or more of said conditions being suggestive or indicative of at least some degree of favorable prognosis.

20. A method to aid in treating cancer of a mucosal/epithelial tissue comprising detecting in a population of cancer cells obtained from said tissue the presence of ERγ.

21. A *in vivo* method to aid in suppressing or inhibiting malignant transformation or progression in a steroid hormone responsive mucosal epithelial cell comprising:

ensuring expression of a TGFβ receptor in said cell sufficient to mediate TGFβ inhibition of neoplastic cell growth;

ensuring expression of at least one receptor chosen from the group consisting of:

a poly-Ig receptor expressed on said cell sufficient to mediate IgA and/or IgM inhibition of steroid hormone responsive growth of said cell in the absence of an inhibition reversing amount of said steroid hormone or steroid hormone mimicking substance; and

a Fcγ receptor expressed on said cell sufficient to mediate IgG1 inhibition of steroid hormone responsive growth of said cell in the absence of an inhibition reversing amount of said steroid hormone or steroid hormone mimicking substance; and

ensuring the availability for binding to said poly-IgR or Fcγ receptor of an immunoglobulin inhibitor of steroid hormone responsive cell growth.

22. A method of inhibiting or arresting *in vivo* cancer cell growth by contacting a steroid hormone responsive mucosal epithelial tissue with a pharmaceutical composition comprising a pharmacologically acceptable carrier and at least one immunoglobulin inhibitor of steroid hormone responsive cell growth chosen from the group consisting of IgA, IgM and IgG1.

23. The method of claim 22 wherein said wherein at least one of said immunoglobulin inhibitors is chosen from the group consisting of dimeric or polymeric IgA, polymeric IgM and IgG1.

24. A method of treating cancer of a mucosal/epithelial tissue that secretes or is bathed by an immunoglobulin, the method comprising enhancing the amount of at least one immunoglobulin inhibitor of steroid hormone responsive cancer cell growth secreted by or contacting said tissue, said at least one inhibitor chosen from the group consisting of IgA, IgM and IgG1.

25. The method of claim 24 further comprising detecting in a population of cancer calls obtained from said tissue the presence of an immunoglobulin inhibition mediating receptor chosen from the group consisting of the poly-Ig receptor, poly-Ig like receptors, and portions thereof.

26. The method of claim 25 further comprising detecting in said population of cancer cells the presence of ERγ.

27. The method of claim 26 further comprising administering to an individual in need thereof an effective amount of an immunoglobulin mimicking substance sufficient to inhibit cancer cell growth.

28. The method of claim 27 wherein said immunoglobulin mimicking substance comprises tamoxifen or a metabolite thereof.

29. A method of inhibiting or arresting growth of a steroid hormone responsive tumor in a mammal comprising administering an immunogen to said mammal in an amount sufficient to induce sufficient plasma and/or mucosal production of at least one secretory immunoglobulin inhibitor of steroid hormone responsive cell growth to inhibit steroid hormone responsive proliferation of a plurality of steroid hormone responsive cancer cells in said mammal.

30. The method of claim 29 wherein said administering comprises orally administering said immunogen.

31. The method of claim 29 further comprising determining an age range for said mammal when native production of said at least one secretory immunoglobulin inhibitor in said mammal is or is expected to be less than a predetermined value.

32. The method of claim 31 wherein said administering comprises administering said immunogen at a predetermined time such that production of said at least one secretory immunoglobulin inhibitor by said mammal during said age range is enhanced.

33. A method of inducing natural mucosal production of cancer deterring factors comprising parenteral administration to a mammal of a sufficient amount of secretory immunoglobulin-stimulating antigen sufficient to induce plasma and/or mucosal production of a predetermined steroid hormone responsive cancer cell growth-inhibiting amount of at least one secretory immunoglobulin chosen from the group consisting of IgA, IgM, and IgG1.

34. A method of enhancing levels of cancer deterring factors in a body fluid bathing a gland or mucosal tissue, the method comprising introducing into the body of an individual in need thereof at least one exogenous steroid hormone responsive cell growth immunoglobulin inhibitor, said at least one inhibitor chosen from the group consisting of IgA, IgM and IgG1.

35. The method of claim 34 further comprising qualitatively and/or quantitatively testing a body fluid or secretion for said at least one inhibitor to confirm immunization.

36. A method of restoring or enhancing immunoglobulin regulation of steroid hormone responsive cell growth in a mucosal epithelial cell comprising restoring or enhancing expression in said cell of a mediator of immunoglobulin inhibition of steroid hormone responsive cell growth.

37. The method of claim 36 comprising enhancing expression of a poly-Ig receptor or a Fcγ receptor by said cell.

38. A method of identifying carcinogenic bacteria in a tissue comprising:

obtaining a bacteria-containing specimen of glandular/mucosal epithelial tissue or body fluid secreted by or bathing a gland or mucosal epithelial tissue;

taking precautions in obtaining and handling said specimen such that contamination by extraneous microorganisms is avoided;

culturing the bacteria in said specimen such that at least one isolated bacterial colony is obtained;

optionally, determining the gram stain negative or gram stain positive classification of said bacterial colonies;

selecting at least one of said bacterial colonies for further examination;

conducting an Ames Test on each selected colony such that mutagen-producing bacterial isolates are identifiable;

optionally, testing said bacterial isolates for production of defined metabolites known to or suspected of being mutagenic;

optionally, testing said bacterial isolates for induction of an oxidative burst when incubated with a neurophil or macrophage;

optionally, testing said bacterial isolates for immunoglobulin protease activity;

optionally, when said fluid comprises a breast secretion, determining whether any said bacterial isolate survives and grows in the presence of a normal bacterial cell inhibiting amount of lactoferrin;

growing a bacterial isolate in a medium;

optionally, after growing said bacterial isolate, testing said medium with a non-tumorigenic human mucosal epithelial cell line such that cells that are altered to a malignant phenotype by a component of said medium are detectable;

optionally, identifying a bacterial isolate using a PCR technique.

39. A method of conferring or enhancing resistance by a mucosal epithelial cell to malignant transformation comprising inducing immunity in a host to at least one bacteria known to or suspected of being oncogenic, as determined according to the method of claim 38.

40. A method of deterring malignant transformation of a mucosal epithelial cell comprising administering an effective amount of an antibiotic to a host infected by an oncogenic bacteria, as determined according to the method of claim 38.

41. A method of preparing an anti-cancer antibody comprising:

selecting at least one bacteria known to or suspected of inducing malignant transformation in mucosal epithelial cells; said selecting comprising identifying said at least one bacteria according to the method of claim 38; and

inducing immunity to said at least one bacteria in an individual considered to be at risk of developing cancer in a tissue comprising said cells.

42. A method of preventing or reducing the risk of developing cancer in a mucosal epithelial tissue comprising immunizing an individual against at least one bacteria known to or suspected of inducing malignant transformation in said tissue, said bacteria being identifiable according to the method of claim 38.

43 The method of claim 42 wherein said immunizing comprises administering an inactivated or attenuated form of said bacteria to said individual by a route chosen from the group consisting of oral, nasal, rectal, such that mucosal immunity against said bacteria is conferred.

44. A method of suppressing an effect of malignant transformation of a steroid hormone responsive epithelial cell comprising enhancing the amount of IgA and/or IgM and/or IgG1 secreted by or contacting said cell sufficient to inhibit steroid responsive growth stimulation of said cell in the absence of a inhibition reversing amount of said steroid hormone or a steroid hormone mimicking substance.

45. The method of claim 44 wherein said steroid hormone responsive epithelial cell is chosen from the group consisting of breast, prostate, oral cavity mucosa, salivary/parotid glands, esophagus, stomach, small intestine, colon, tear ducts, nasal passages, liver and bile ducts, bladder, pancreas, adrenals, kidney tubules, glomeruli, lungs, ovaries, fallopian tube, uterus, cervix, vagina, and secretory anterior pituitary gland cells.

46. A method of detecting previous or active infection by a bacteria known to or suspected of being oncogenic in mucosal epithelial tissue, the method comprising detecting in plasma or a body fluid or

secretion an antibody against said bacteria, said bacteria being identifiable according to the method of claim 38.

47. A method of preventing or reducing the risk of occurrence of cancer of a mucosal epithelial tissue comprising administering to a mammalian subject in need thereof at least one of the following treatments:

administering an antibiotic active against at least one bacteria known to or suspected of inducing malignant transformation in mucosal epithelial cells, said bacteria being identifiable according to the method of claim 38;

administering an immunogen to said subject in an amount sufficient to induce plasma and/or mucosal production of at least one secretory immunoglobulin inhibitor of steroid hormone responsive cell growth sufficient to inhibit steroid hormone responsive proliferation of a plurality of steroid hormone responsive cancer cells in said mammal;

administering at least one immunoglobulin inhibitor of steroid hormone responsive cell growth in an amount sufficient to inhibit or arrest steroid hormone responsive growth of said cells.

48. A method to aid in deterring development of a steroid hormone responsive tumor in a mammal comprising enhancing plasma and/or mucosal production of at least one immunoglobulin inhibitor of steroid hormone responsive cell growth.

49. The method of claim 48 wherein said enhancing comprises administering to said mammal an immunogen capable of inducing production of at least one immunoglobulin inhibitor of steroid hormone responsive cell growth.

50. The method of claim 48 further comprising determining an age range of said mammal when native production of said at least one immunoglobulin inhibitor in said mammal is less than a predetermined value.

51. The method of claim 48 wherein said enhancing comprises increasing the plasma and/or mucosal concentration of said at least one immunoglobulin inhibitor during said time interval.

52. A method of arresting cell proliferation of an early, steroid hormone responsive mucosal epithelial malignancy comprising contacting a population of malignant mucosal epithelial cells with an effective amount of an immunoglobulin inhibitor chosen from the group consisting of IgA, IgM and IgG1, and combinations thereof.

53. A pharmaceutical composition comprising at least one immunoglobulin inhibitor of steroid hormone responsive cell growth and a pharmacologically acceptable carrier.

54. The composition of claim 53 wherein said cell is a mucosal epithelial cell.

55. The composition of claim 54 wherein said cell is a cancer cell.

56. The composition of claim 53 wherein said at least one immunoglobulin inhibitor is chosen from the group consisting of IgA, IgM and IgG1.

57. The composition of claim 56 wherein at least one said immunoglobulin inhibitor is chosen from the group consisting of dimeric IgA, polymeric IgA, polymeric IgM and IgG1κ.

58. The composition of claim 53 further comprising at least one immunoglobulin-mimicking substance.

59. The composition of claim 58 wherein said immunoglobulin-mimicking substance comprises tamoxifen or a metabolite thereof.

60. A mediator of steroid hormone reversible IgA, IgM of IgG1 inhibition of steroid hormone responsive cell growth comprising a poly-Ig receptor or a Fcγ receptor.

61. An expression vector for gene replacement therapy in a mammalian cell to restore or enhance expression of an immunoglobulin inhibition mediating receptor, said vector comprising a DNA sequence encoding a receptor chosen from the group consisting of poly-Ig receptor, Fcγ receptor, and biologically active subunits and variants thereof, operably linked to a promoter capable of functioning in a preselected mammalian mucosal/epithelial target cell.

62. The expression vector of claim 61 further comprising a DNA sequence encoding a TGFβ receptor, or a biologically active subunit or variant thereof, operably linked to a promoter functional in said target cell.

63. A method of expressing a mediator of immunoglobulin inhibition of steroid hormone responsive cell growth comprising introducing the expression vector of claim 61 into said mammalian cell and allowing said cell to express said DNA sequence.

64. The method of claim 63 further comprising introducing into said cell an expression vector comprising a DNA sequence encoding a a TGFβ receptor, or a biologically active subunit or variant thereof, operably linked to a promoter capable of functioning in said cell.

65. A method of treating a breast cancer patient, said cancer containing, or suspected of containing, a mixed population of steroid hormone responsive cancer cells and autonomous cancer cells, the method comprising:

administering at a surgical site an amount of an iron depleting substance sufficient to substantially deprive said autonomous cells of a cell growth supporting concentration of Fe (III);

maintaining a Fe (III) depleted environment at said site for a predetermined period of time sufficient to inhibit cell growth and/or kill said autonomous cancer cells;

administering at said site an amount of a Fe (III) containing substance sufficient to inhibit cell growth and/or kill said steroid hormone responsive cells;

maintaining a Fe (III) enhanced environment at said site for a predetermined period of time sufficient to inhibit cell growth and/or kill said steroid hormone responsive cancer cells; and,

optionally, administering at said site an amount of immunoglobulin inhibitor sufficient to inhibit proliferation of said steroid hormone responsive cells.